Biliary and Gastrointestinal Manifestations of the Herpes Simplex Virus, Type I (HSV-I)

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Abstract

Objective: To analyze 421 surgical patients exhibiting biliary and gastrointestinal dysfunction over a seven year period. We theorized that the cause for these disorders was the Herpes Simplex Virus I and treated a carefully selected subset of patients.

Methods: A gastrointestinal questionnaire was administered to 193 patients who exhibited the most complex symptoms and several obvious patterns were noted. We explained our theory to the 74 most symptomatic patients, and they agreed to take antiviral medication. The length of therapy ranged from 6 to 40 months. To confirm the success of the therapy a research institute independently administered a follow-up questionnaire.

Results: The success of treatment was remarkable, and further validated by the following anonymous survey results: patients felt healthier 3 to 1; they felt more energetic 2 to 1, moreover, they recovered from illnesses faster nearly 4 to 1. They also reported the following changes in symptoms: less bloating 4 to 1, less abdominal pain 2 to 1, less diarrhea more than 4 to 1, fewer headaches nearly 2 to 1, improved reflux symptoms 3 to 1, in addition, less constipation 5 to 1.

Conclusion: The results of this study and the human DNA studies of Gesser and Koo suggest that some chronic gastrointestinal and biliary diseases may be caused by HSV-I. Randomized double-blinded studies are needed to validate this hypothesis.

Introduction

With the exception of ocular disease and encephalitis, the pathologic role of HSV-I is largely unknown. The virus is generally felt to represent nothing more than a nuisance that causes the
occasional fever blister. General surgeons frequently encounter patients suffering from acalculus cholecystitis, GERD, gastroparesis, irritable bowel disease, and colonic inertia. Three years ago, we began to suspect that HSV-I had an adverse effect on the gastrointestinal system. Observing similar trends when interviewing patients, we began our initial research. We repeatedly observed a cyclical deterioration of their health, which led us to suspect a common etiology, possibly viral in origin. The most likely DNA virus was the HSV-I type. Gesser and Koo\textsuperscript{1,2} have documented the presence of HSV-I DNA in the vagus nerve (nodose) ganglion of animal and human subjects. The objective of our study was to identify patients who suffered from these chronic gastrointestinal conditions and offer them antiviral medications with the goal of ameliorating their symptoms and diseases. Our study was very much an observational project. This paper presents the background research and personal experiences that led us to formulate our hypothesis, and chronicles the results of the initial questionnaire and treatment outcomes of our patients.

**Methods**

Tuscaloosa Surgical Associates, P.C. retrospectively analyzed charts of 400 patients between the ages of 18 and 75, who underwent a cholecystectomy or a nissen fundoplication beginning June 29, 1999. Twenty-one additional patients who fit the study profile were included over the last six months prior to March 31, 2006, the deadline for finalizing the study group. One hundred ninety-three patients were ultimately selected for the study population, based on subjective criteria and combinations of symptoms including GERD, chronic nausea, bloating, fatigue, frequent headaches, chronic diarrhea and/or constipation. All patients in the study group have several of these symptoms, a history of gallbladder or reflux surgery, previous diagnosis of irritable bowel disease, or colonic inertia. Eighty-five of the 193 patients who completed the
questionnaire underwent viral testing for HSV-I/II IgG, HSV-II type specific IgG, and EBV. A subjective gastrointestinal history questionnaire with an informed consent section was completed and signed by each patient with the understanding that his/her information might be used in a research project. Letters were sent to all area physicians notifying them of the research study. A cohort of 74 of the 193 patients with the most severe symptoms or an obviously deteriorating course was selected; 62 had undergone testing. (Twelve indigent patients opted not to undergo testing because of the expense, and only 2 patients who fit the profile declined to participate.) The 74 patients were offered treatment with one of three antiviral medicines (valacyclovir 500mg twice daily, acyclovir 400mg twice daily, or famciclovir 250mg twice daily). Patients were treated regardless of their ability to pay. The patients were informed that they might still become ill, but that the severity would be less and their deterioration might diminish or even stop. Later we began to treat non-operative and peri-operative patients as well. They were evaluated in the office every 1-2 months to monitor therapy effectiveness. To date follow-up viral titers have not been repeated.

An Institutional Review Board (IRB) committee of the University of Alabama Institute for Rural Health Research (IRHR) assisted with the study and all authors successfully completed an ethics and medical research online test. Given the highly subjective nature of this study, a follow-up survey conducted by the IRHR gave each patient the option of completing an anonymous questionnaire online or mailing the results to the University. The IRHR independently evaluated the results.

**Results**

We selected our study population by subjectively analyzing the histories and operative findings of 421 charts to determine which combination of criteria might suggest nodose ganglion
dysfunction. A total of 193 patients were selected as study subjects. They completed the questionnaire and the results are displayed (figure 1). Acalculus cholecystitis and/or biliary dyskinesia in an otherwise healthy individual was the strongest predictor of a successful response to antiviral medications, followed by irritable bowel symptoms. When the lesser indicators of GERD, bloating, chronic tension headaches (etiology less clear), the non-diabetic patient with unexplained gastroparesis and colonic inertia were added, certain patterns began to form. These three patterns included: Type I, which suggested proximal gut involvement and exhibited symptoms of GERD, gallbladder disease, bloating, nausea, headache, and diminished energy; Type II, which suggested midgut involvement, and displayed symptoms of nausea, irritable bowel symptoms including diarrhea alternating with constipation, bloating, headaches, and diminished energy; Type III patients exhibited nausea, chronic constipation, (often going 3-4 weeks without a bowel movement, i.e. colonic inertia), bloating, headaches, and a lack of energy. Of the 76 established surgical patients to whom we offered treatment, only two declined. Eighty-eight percent of the patients who underwent viral testing tested positive for HSV I/II IgG. There was no commercially available HSV I IgG test available through our area labs.

Interestingly, many patients experienced viral symptoms around 7-10 days after a surgical procedure, whether they were on treatment or not. However, the postoperative viral symptoms: fatigue, headache, nausea, and bloating were of shorter duration and magnitude on therapy. Following the 2-3 day illness, patients perceived an overall sense of improved health and heightened energy. The follow-up questionnaire administered by the University of Alabama Institute for Rural Research produced a 38 percent response rate and results shown in figure 2.
Discussion

Chronic biliary and gastrointestinal disorders such as biliary dyskinesia (acalculus cholecystitis), GERD, gastroparesis, irritable bowel disease, and colonic inertia have become a source of growing frustration for physicians. Despite appropriate medications and surgery, this patient population frequently complained of a continued general decline in health. This often led to “doctor shopping,” embracing non-traditional forms of medicine, and/or patients questioning their own sanity. After years of frustration, I began to discern a commonality in the patients’ profiles and the cyclical occurrences of their conditions. The frequency of the occurrences shared a similarity with the patterns of the HSV-I virus. The HSV-I virus is a DNA virus of the Herpes virus family, which also includes Herpes Zoster, HSV Type II, EBV, and CMV. All are frequently acquired and unfortunately remain in the nucleus as a nonintegrated circular DNA molecule associated with nucleosomes. It is widely known that HSV-I may enter the body through the eyes, nose, or oral mucosa. It can also enter through the mucosal surfaces of the genital region. HSV-I exhibits tropism for the peripheral processes of neurons that innervate these body surfaces. It is then transported to the nerve cell nucleus located in the sensory ganglia. Prior research has shown these to include the trigeminal ganglion and the sacral dorsal root ganglion. Recent work by Gesser & Koo\textsuperscript{1, 2} supported the concept of additional involvement of the ganglion of the vagus nerve known as the nodose ganglion, and postulated the potential for apoptotic destruction of the ganglion over time.

Their work at the Children’s Hospital in Philadelphia showed that HSV-I, when inoculated into the esophageal lumen of mice, travels to the sensory ganglion of the vagus nerve. Gesser and Koo postulated that HSV-I was an enterically acquired pathogen able to breach the mucosal surface of the gut and invade the nerve fibers of the enteric nervous system. HSV-I infected
neurons of the mesenteric, submucosal, and periglandular plexuses of the esophagus, stomach, and duodenum without significant spread to surrounding tissues. “These new findings in immunocompetant hosts indicate that HSV-I, previously not considered an enteric pathogen spreads considerably within all levels of the enteric nervous system including nerve fibers in contact with the mucosal epithelium.”¹ Their research suggested that the spread was very specific to the nerve inoculation site, and not via the circulatory system. They found that HSV-I preferentially used sensory fibers originating in the nodose ganglion and terminating centrally in the nucleus tractus solitarius. Describing the development of erosive gastric and esophageal mucosal ulcers in mice, they noted that these ulcers were not directly infected, but were found to overlay virus-infected enteric ganglia. They hypothesized that “latent or reactivated HSV-I enteric nervous system infection may also be involved in the pathogenesis of chronic, recurrent functional human gastrointestinal disorders.”¹

In a later publication involving humans used in situ hybridization, Gesser and Koo demonstrated that latent HSV-I gene expression is prevalent in human adult nodose ganglia. They suggested that the infection of gastrointestinal sensory nerves, probably through swallowed virus-laden oral secretions, occurs commonly and that HSV-I reactivating from the site may play a role in recurrent gastrointestinal disorders.² Ninety-eight percent of the participants in a recent study were found to have HSV-I shedding. Although a blood test disclosed only 74 percent of these participants, the rest were confirmed by analyzing saliva and tears. The fact that HSV-I DNA was discovered in such a high percentage of healthy people in the general population tells us that the virus is everywhere and it is unavoidable.³

Systemic antiviral medication (Famvir) has been used to suppress HSV-I reactivation in HIV infected persons in a double blind placebo-controlled trial. “Among the 20 participants with the
antibodies to HSV-I, seven (35 percent) shed HSV-I only while receiving placebo, one (5 percent) shed HSV-I only while receiving famciclovir. Shedding of HSV-I occurred on 26 of 1084 placebo days (2.4 percent) and 6 of 1053 famciclovir days (0.6 percent). Famciclovir reduced the percentage of days with oral symptoms from 7.3 percent with placebo to 1.3 percent with famciclovir. The reductions in shedding and symptoms were statistically significant (P=0.02 for both). Famciclovir (a nucleoside analogue) is the oral formulation of pencyclovir, and is a selective substrate for the HSV-I, HSV-II and varicella zoster virus thymidinekinase. It allows cellular enzymes to produce pencyclovir triphosphate, which selectively inhibits the viral DNA polymerase. Famciclovir was well tolerated and no patients discontinued the treatment due to side effects. Acyclovir (Zovirax) and valacyclovir (Valtrex) are equal in efficacy and famcyclovir (Famvir) has the added advantage of being a smaller tablet.

Historically the antivirals have a low incidence of adverse reactions, and no patient in our study stopped the medicine due to side effects. Interestingly, the reported side effects (nausea and vomiting, fever, fatigue, and headaches) are the same symptoms of a viral reactivation. Hemolytic anemia and TTP, as well as phlebitis, nephrotoxicity, and CNS changes are rarely reported side effects for some of these medicines.

Only recently have studies surfaced examining not only the efficacy, but also the safety of long-term anti-viral medication for the treatment of HSV-I disease. A recent report from Will’s Eye Hospital, Jefferson Medical College, and Thomas Jefferson University retrospectively analyzed ocular herpes simplex virus recurrence in two groups of patients treated for more than 12 months. Discontinuation of antiviral medication (acyclovir) resulted in a statistically different rate of recurrence. Both Famvir and Valtrex are primarily indicated for the episodic and
suppressive treatment of recurrent genital herpes. Valtrex has an indication for treating HSV-I cold sores.

This is the first clinical study in the literature that takes information from the studies cited above and applies it to a population suffering from chronic gastrointestinal and biliary conditions. We hypothesized that the portion of the GI tract where the initial viral inoculation site occurred determined which patterns the patient would exhibit. We envision three separate regions of the ganglion were affected: (1) the proximal segment controlled the esophagus, gallbladder, and stomach; (2) the middle segment controlled the stomach and small bowel; and (3) the distal segment controlled the colon. The patterns we noted were akin to looking at a “Magic-eye” (a coffee table text of visual puzzles). These are difficult to visualize at first, but once one sees the patterns, one will always see them. These patients have been some of the most difficult to manage because they never get entirely well and their slow deterioration is frustrating to all. However, after they are given an explanation of why they feel the way they do and when they are on therapy, these patients are much easier to manage.

Our results showed that treated patients felt they were healthier on antivirals nearly 3 to 1 and those patients who felt they had more energy outnumbered those who did not nearly 2 to 1. Additionally, patients who felt that they recovered from illnesses faster on antiviral medicines outnumbered those that did not 4 to 1. The patients on treatment experienced less bloating, less abdominal pain, less diarrhea, fewer headaches, improved reflux symptoms, and less constipation. Finally, the number of patients who felt the benefits of the antiviral medications outweighed the cost was 2.4 times more numerous. (figure 2) This data used descriptive analysis due to a lack of a control group. The usual 40 percent benefit that can be achieved with placebos cannot begin to explain these results.
The next step is to begin a randomized double-blind study comparing placebo to treatment with antiviral medications. Each indicator will be assigned a value so there is some standardization of the selection process. Although The University of Alabama has expressed interest in pursuing a study of this type, it would be preferable if this were a multi-institutional collaboration. Should the double-blind study prove our findings, perhaps there will be a new sense of urgency to create a vaccine for HSV-I, as well as better medications. According to the website of Glaxo Smith Kline, phase three trials are currently underway for an HSV II vaccine. The bovine industry and their veterinarians are very close to creating an effective vaccine for BHV-I, a close cousin to the HSV-1 and a member of the alphaherpesvirinae subfamily.6 This industry loses $500 million annually in the United States alone, because of illnesses attributed to the BHV-I virus. The monetary impact for HSV-1 diseases may in all likelihood dwarf this number considerably.
Figure 1. Breakdown of the results of the initial GI questionnaire for the 193 patients questioned.
Figure 2. Patient responses to the gastrointestinal and biliary follow up questionnaire administered by the Institute for Rural Health Research, Tuscaloosa Alabama.
References


